IN THE EUROPEAN PATENT OFFICE

Applicant: Omeros Corporation, et al.

European Application No: 00 947581.5

Int'l. Filing Date: 21 July 2000 (21.07.00)

Title: SOLUTIONS AND METHODS FOR INHIBITION OF PAIN, INFLAMMATION AND CARTILAGE DEGRADATION

Agent's File Reference No. APEP01999

DECLARATION OF MARTIN LOTZ, M.D.

I DO HEREBY SOLEMNLY AND SINCERELY DECLARE AS FOLLOWS:

1. I, Martin Lotz, M.D., am a Research Professor, Department of Medicine, University of California, San Diego, and Professor, Department of Molecular and Experimental Medicine, as well as Head, Division of Arthritis Research, The Scripps Research Institute, La Jolla. I obtained my Medical Degree from the Universities of Marburg, Vienna and Heidelberg, and completed my residency in internal medicine at University Hospital, Heidelberg. I am, and for the last 20 years have been, active in research and clinical practice in specialties including rheumatic diseases, osteoarthritis and other joint diseases. I have authored or co-authored over 150 publications in refereed journals in these fields, and serve on the editorial boards of *Arthritis & Rheumatism, Osteoarthritis & Cartilage, The Journal of Immunology, Revue de Rhumatisme, Biotherapy* and *Modern Rheumatology*. I am the President-Elect of the Osteoarthritis Research Society and serve on the board of Directors of the Osteoarthritis Research Society. As part of my academic, research and hospital responsibilities, I supervise and train academicians and clinicians of less experience in my specialties. My *curriculum vitae,* including a bibliography of publications, is attached.

2. I have reviewed and am familiar with the disclosure and claims contained in European Patent Application 00 947581.5 (the "Application"), corresponding to International Patent Application PCT/US00/19864. I have been asked to express my opinions regarding certain scientific terms used in the Application. These terms include: "chondroprotective agent"; "anabolic chondroprotective agents" (also referred to in the Application as "agents that promote cartilage anabolism"); and "inhibitors of cartilage catabolism" (also referred to in the Application as "agents that inhibit unregulated or excess cartilage catabolic processes"). Specifically, I was

asked to express my opinion on whether these terms would have been readily understood and considered to be definite by one of ordinary skill, experience and expertise in the relevant scientific field, in view of the disclosure set forth in the Application, and based on public knowledge available to such individuals as of 21 July 1999. I was also asked whether such individuals would readily be able to determine whether a given therapeutic agent was an anabolic chondroprotective agent, or an inhibitor of cartilage catabolism, in view of the disclosure set forth in the Application, and using public knowledge available to such individuals as of 21 July 1999, without undue experimentation.

3. I provide the following opinions based on my personal knowledge and in view of the disclosure set forth in the Application.

a. Definitions of the terms "anabolic" and "catabolic" in the context of cartilage metabolism and joint disease were familiar to anyone in broad clinical fields such as general medicine, internal medicine, rheumatology and orthopedics, and to the scientific communities engaged in arthritis research.

i. "Cartilage catabolism" was known as the degradation of existing cartilage extracellular matrix and/or the loss of cartilage cells. A drug that interferes with this process was commonly understood as an "inhibitor of cartilage catabolism." (1,3).

ii. "Cartilage anabolism" was commonly understood as the new synthesis of cartilage extracellular matrix and/or chondrocyte proliferation. (1,3,4). A drug that promotes these processes was commonly referred to as an "anabolic agent."

b. The term "chondroprotection" was understood as a process that improves or maintains cartilage structure and function. This could result from either stimulation of anabolic responses or inhibition of catabolic responses. A definition of "chondroprotection" as either the stimulation of anabolic responses or the inhibition of catabolic responses, and a definition of a "chondroprotective agent" as a drug that affects these processes, follows from the above statement. Similar definitions can be found in the literature. (7,8).

c. Methods that characterize biological effects of a drug on chondrocytes and/or cartilage to classify it as an anabolic agent have been published and widely used. No proprietary technologies were required. Known assays for anabolic activities include measurements of new extracellular matrix synthesis such as collagens and proteoglycans, and of chondrocyte proliferation by conventional radio-thymidine incorporation. (4,5,6,9,10). The most likely methods to be selected include assays of chondrocyte proliferation and synthesis of cartilage extracellular matrix molecules, including glycosaminoglycans, aggrecan or collagens.

d. The list of agents provided in the Application provides an accurate classification of many examples of anabolic agents.

e. "Cartilage catabolism" was known as the degradation of cartilage extracellular matrix and/or loss of cartilage cells. A drug that interferes with this process was commonly understood as a chondroprotective agent that is an "inhibitor of cartilage catabolism". Methods that characterize biological effects of a drug on chondrocytes and cartilage to classify it as an inhibitor of catabolism have been published and widely used. No proprietary technologies were required. In these assays, cartilage or chondrocytes are stimulated with a known catabolic factor (such as Interleukin-1). A catabolic inhibitor would prevent the induction of matrix metalloproteinases and proinflammatory mediators by IL-1, or cellular and molecular events associated with chondrocyte activation by a catabolic factor. (2,6). It follows that a catabolic inhibitor would be tested in chondrocytes that are activated by IL-1. The assay would determine whether the catabolic inhibitor antagonizes the IL-1-mediated induction of inflammatory mediators (nitric oxide, prostaglandins, cytokines) or matrix degrading enzymes (collagenases, aggrecanases), and whether the catabolic inhibitor reverses the IL-1-mediated inhibition of extracellular matrix synthesis.

f. The list of agents provided in the application provides an accurate classification of many examples of catabolic inhibitory agents.

g. Current concepts and opinions at the time (July 21, 1999) were focused on the development of compounds that specifically and selectively target molecules and processes involved in cartilage catabolism, or that stimulate anabolic responses. (6). The role of cytokine-driven anabolic and catabolic processes in maintaining the integrity of articular cartilage was recognized by researchers in the field of osteoarthritis for years prior to that time. (1, 3, 10). Despite this long-standing awareness of compounds affecting these two types of processes, the combined local (e.g., intraarticular) use of an anabolic chondroprotective agent together with a catabolic inhibitor had not been tested or proposed.

4. I make this solemn declaration conscientiously and sincerely believing the same to be true.

5. In the event that a copy of this declaration should ever be filed in any corresponding United States Patent Application, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful, false statements and the like that are so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

DATED this 14th day of April, 2003.

Martin Lotz, M.D.

References cited in Declaration of Martin Lotz, M.D.

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CURRICULUM VITAE

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Education and Professional Experience:

1974-1980	Medical School, Universities of Marburg, Vienna and Heidelberg
1980-1982	Internship and Residency in Internal Medicine University Hospital, Heidelberg
1983-1987	Research Associate Department of Basic and Clinical Research Scripps Clinic and Research Foundation, La Jolla, California
1986-1988	Clinical Rheumatology Fellowship University of California, San Diego
1987-1990	Assistant Member Department of Molecular and Experimental Medicine Scripps Clinic and Research Foundation, La Jolla, California
1990-1996	Adjunct Assistant Member Department of Molecular and Experimental Medicine The Scripps Research Institute, La Jolla, California
1990-1996	Associate Professor of Medicine University of California, San Diego
1997-present	Research Professor, Department of Medicine University of California, San Diego
1997-present	Professor, Department of Molecular and Experimental Medicine Head, Division of Arthritis Research The Scripps Research Institute, La Jolla, California

HONORS:
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Board of Directors, Osteoarthritis Research Society 2000-
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PROFESSIONAL ORGANIZATIONS:
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American College of Rheumatology
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EDITORIAL BOARDS:
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GRANT REVIEWS:
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CLINICAL ACTIVITIES:
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